

CLAIMS

1. A method for identifying inhibitor compounds capable of reducing the interaction between:
- 5 a) a first region which is a signature motif on a nuclear protein, and
b) a second region which is that part of a nuclear receptor which is capable of interacting with the nuclear protein through binding to the signature motif,
wherein:
the nuclear protein is a bridging factor that is responsible for the interaction between a
10 liganded nuclear receptor and a transcription initiation complex involved in regulation of gene expression;
the nuclear receptor is a transcription factor;
the signature motif is a short sequence of amino acid residues which is the key structural element of a nuclear protein which binds to a liganded nuclear receptor as part of the process
15 of the activation or repression of target genes; and
in which the method comprises taking:
i) the potential inhibitor compound;
ii) the liganded nuclear receptor or a fragment thereof in which the fragment comprises the second region defined in this claim in b) above;
20 iii) a fragment comprising a signature motif of the nuclear protein; and
iv) detecting the presence or absence of inhibition of the interaction between ii) and iii).
- 2 A method according to claim 1 in which the signature motif is B¹XXLL in which B¹ is any natural hydrophobic amino acid, L is leucine and X independently represents any natural amino acid.
- 25 3 A method according to claim 2 in which B¹ is leucine or valine.
4 A method according to claim 3 in which B¹ is leucine.
5 A method according to any one of claims 2-4 in which the signature motif is further defined as B²B¹XXLL wherein B² is a hydrophobic amino acid.
6 A method according to claim 5 in which B² is selected from the group consisting of
30 isoleucine, leucine, methionine, phenylalanine, tryptophan, tyrosine and valine.

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7. A method according to any one of claims 1-6 in which the nuclear protein is a coactivator.
8. A method according to claim 7 in which the coactivator is selected from the group consisting of RIP 140, SRC-1, TIF2, CBP, p300, TIF1, Trip1, Trip2, Trip3, Trip4, Trip5, Trip8, Trip9, p/CIP, ARA70 & Trip230.
- Sub 94
9. A method according to any one of claims 1-6 in which the transcription factor is a steroid hormone receptor.
10. A method according to claim 9 in which the steroid hormone receptor is selected from the group consisting of oestrogen receptor, progesterone receptor, androgen receptor and glucocorticoid receptor.
11. A method according to claim 10 in which the steroid hormone receptor is oestrogen receptor.
12. A method according to any preceding claim wherein the method is in the form of a 2-hybrid assay system.
13. A method according to any preceding claim wherein the potential inhibitor is in the form of a peptide library based on a signature motif as defined in any one of claims 2-6.
14. A novel inhibitor identified according to the method defined in any one of claims 1-13 which reduces the interaction between
- a) a first region which is a signature motif on a nuclear protein, and
- b) a second region which is that part of a nuclear receptor which is capable of interacting with the nuclear protein through binding to the signature motif,
- wherein:
- the nuclear protein is a bridging factor that is responsible for the interaction between a liganded nuclear receptor and the transcription initiation complex involved in regulation of gene expression;
- the nuclear receptor is a transcription factor;
- the signature motif is a short sequence of amino acid residues which is the key structural element of a nuclear protein which binds to a liganded nuclear receptor as part of the process of the activation or repression of target genes.
15. An inhibitor according to claim 14 which is a peptide of less than 15 amino acid residues comprising the signature motif defined in any one of claims 1-6.
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18 A pharmaceutical composition which comprises an inhibitor as defined in any one of claims 14-17 or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

19 A method of mapping nuclear receptor interaction domains in nuclear proteins in
20 which the method comprises analysis of the sequence of a nuclear protein for the presence of
21 signature motifs as defined in any one of claims 1-6 in order to identify an interaction domain
22 or a potential interaction domain.

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